CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215341Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 215341: Kerendia (Finerenone) Tablets

Integrated Quality Review

Recommendation: Approval

Product Name	Kerendia (finerenone) tablets, for oral use
Indication	To [redacted] (b) (4) reduce the risk of [redacted] (b) (4) cardiovascular [redacted] (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes
Strength	10 and 20 mg
Dosage Form	Oral Tablets
Rx/OTC Dispensed	Rx
Applicant	Bayer HealthCare LLC
Submissions (s) Reviewed	NDA 215341 and all the submitted CMC amendments

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Zhengfu Wang	OPQ/ONDP/DNDAPI/NDB3
Drug Product	Ali Mohamadi	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Ke Ren	OPQ/OPMA/DPMAII/PMB6
Biopharmaceutics	Jing Li	OPQ/ONDP/DB/BB3
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams (OPQ/OPRO/DRBPMI/RBPMB2)

Related/Supporting Documents:

Document	Application Number	Description
NA	NA	NA

CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 215341 (Kerendia (Finerenone) Tablets), is recommended for approval. Based on the stability data submitted to date, the expiry dating period for Kerendia (finerenone) tablets shall be 36 months from the date of manufacture, when stored at controlled room temperature (USP) of 20°C to 25°C (68°F to 77°F) in the purposed commercial packaging. Excursions are permitted from 15°C to 30°C (59°F to 86°F).

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

N/A

II. Quality Assessment Summary

1. Background: The Applicant has sought U.S. marketing approval for Kerendia (finerenone) tablets, for oral use, under the provisions of Section 505(b)(1) of the Federal Food and Cosmetic (FDC) Act. Finerenone (BAY 94-8862) is a nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR) that is claimed to attenuate inflammation and fibrosis mediated by MR overactivation. The MR is expressed in the kidneys, heart and blood vessels. The proposed starting dose is 10 mg or 20 mg, based on eGFR. Dose adjustment during the course of treatment is based on eGFR and serum potassium levels. The maximum daily dose of Kerendia is 20 mg.

2. Drug Substance (Finerenone): The drug substance is practically insoluble in water. (b) (4) drug substance is used for product manufacturing. The (b) (4) (b) (4) specified impurities in the drug substance are controlled below ICH Q3A qualification threshold. The potential genotoxic impurities are adequately controlled. (b) (4) is controlled with a specification limit of NMT (b) (4) ppm; there is no risk of (b) (4) in this process. The fate and purge studies to track potential impurities are adequate. The designation of starting materials is adequately justified. The drug substance specification includes testing of all critical qualities (CQAs), including assay and purity, enantiomeric purity, particle size distribution and residual solvents. Regarding potential elemental impurities, the manufactured batches have been monitored per ICH Q3D, option 1 criteria; none of the Class 1, 2A, 2B and

Class 3 elemental impurities have been found above (b) (4)% of permitted daily exposure thresholds levels. Non-compendial methods are adequately validated. The stability data support a (b) (4) retest period.

3. Drug Product (Finerenone Tablets)

3.1. Product Design, and Release Specification:
Finerenone is formulated as immediate-release tablets with (b) (4) film coating, for oral once daily administration, in the dose strengths of 10 mg and 20 mg. All excipients are USP-NF except the film-coating agent, (b) (4). Enantiomeric purity is not affected by the drug product manufacturing process or product storage. The product release specification involves adequate testing of all the product critical quality attributes (CQAs). The non-compendial methods are validated. Specifically, the degradation product, (b) (4) is controlled by product specification with an acceptance limit of NMT (b) (4)%, which is within ICH Q3B identification threshold for a maximum daily dose of 20 mg. No (b) (4) is used to manufacture the drug product, and the Applicant has provided a risk assessment study to demonstrate that (b) (4), originating from the drug substance and excipients, stay within ICH Q3C thresholds levels. Regarding elemental impurities, the elemental impurities (b) (4) (b) (4) stay within their permitted daily exposure thresholds, as specified in ICH Q3D. Hence, omission of release testing of the product batches for (b) (4) and elemental impurities is justified. The drug product is to be presented in high-density polyethylene (HDP) bottle with a (b) (4) closure and aluminum seal. Based on the information provided, the proposed container closure system is adequate for the intended use.

3.2. Manufacturing: (b) (4) (b) (4) (b) (4) Three registration batches of each strength have been manufactured using the proposed commercial process. The identified critical process parameters and in-process controls are adequate. Overall, the product manufacturing is well-controlled.

3.3. Microbiological Aspects: The drug product batches are adequately tested on release for microbial purity, which involves testing for total aerobic microbial count, combined yeast/mold count and Escherichia coli.

3.4. Biopharmaceutics Aspects:

The Biopharmaceutics review focused on evaluating a) the dissolution method and acceptance criterion for quality control of the proposed product, and b) the bridging of the formulations, used throughout development, and the proposed commercial product.

Dissolution Method and Acceptance criterion: The proposed dissolution method is adequate. Specifically, to further mitigate the risk and to enhance the discriminating ability of the method, the Applicant tightened the acceptance criterion as per FDA recommendation (Q= (b) (4) % in 15 min). The tightened acceptance criterion together with the proposed dissolution method are able to reject the batches manufactured with drug substance having out-of-specification particle size (i.e., D90= (b) (4) µm).
Formulation Bridging: There is a minor difference (b) (4) between the proposed commercial formulation and the phase III formulation manufactured in commercial scale. Bridging between the two formulations is adequately supported by the dissolution data, which indicate that all batches are conforming to the regulatory specifications. The Applicant provided comparative dissolution data for the clinical batches and the commercial batches, which further support the bridging.

3.5. Stability, Storage Conditions and Expiration Date: Based on stability studies, the Applicant has demonstrated product stability for a period of 36 months at long-term storage conditions (25°C /60% RH and 30 °C/75 % RH) and for 6 months at accelerated storage conditions (40°C/75%RH), when stored in the commercial container closure system. The product stability data support: a) an expiry dating period of 36 months when stored at controlled room temperature (USP) of 20°C to 25°C (68°F to 77°F) in the purposed commercial packaging, and b) excursions from 15°C to 30°C (59°F to 86°F).

III. Assessment of Manufacturing Facilities: Regarding the listed manufacturing and testing facilities, there are no outstanding deficiencies and are deemed acceptable. Specifically, the drug product and drug substance manufacturing and testing facilities have been approved based on inspection history and manufacturing experience of the concerned facilities.

1V. Overall Control Strategies: From the quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, and stability.

V. Environmental Assessment

The Applicant has claimed categorical exclusion under 21 CFR Part 25.31(b), which is acceptable.

VI. Product Quality Labeling Recommendations

The product quality recommendations are included in the latest version of labeling, including the Prescription Information.

VII. Life Cycle Knowledge Information

Final Risk Assessment

NDA 215341: Kerendia (Finerenone) Tablets

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay, Stability	• Formulation • Container closure • Impurity exceeding specification • Process parameters • Scale/ equipment/ site	Low (L)	The product CQAs such as identification, assay, and impurity levels, are controlled by appropriate release specification using validated analytical methods. Product stability has been demonstrated for a period of 36 months when stored at 20°C to 25°C in the commercial packaging.	Acceptable	.
Solid state Polymorphic form)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Moderate (M)	(b) (4)	Acceptable	N/A
Content Uniformity	• Formulation • Particle size • Segregation • Raw materials • Process parameters • Scale/ equipment/ site	Moderate (M)	Particle size (b) (4) (b) (4) controlled by release specification. Product content uniformity is tested on release.	Acceptable	Any proposed changes to formulation, manufacturing, or the control strategy will need to be evaluated for possible impact on content uniformity.

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Poor Adhesion Related Delamination (for multilayered tablets	• Formulation • Process parameters • Scale/equipment/site	Low (L)	The manufacturing process (b) (4) controls are adequate (b) (4) (b) (4)	Acceptable	
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment/site • API sources	Moderate (M)	Dissolution monitored on release. The dissolution method has adequate discriminating ability towards critical attributes.	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equipment/site	Low (L)	(b) (4) (b) (4) The drug product tested on release for microbial purity.	Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 215341 is recommended for approval. Based on the stability data submitted to date, the expiry dating period for Kerendia (finerenone) tablets shall be 36 months from the date of manufacture, when stored at controlled room temperature (USP) of 20°C to 25°C (68°F to 77°F) in the purposed commercial packaging. Excursions are permitted from 15°C to 30°C (59°F to 86°F).

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead; Division of Cardiology and Nephrology
CDER/OPQ/ONDP/DNDPIII/NDPB5

75 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	KERENDIA	Adequate
Established name(s)	finerenone	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablet, 10 mg or 20 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

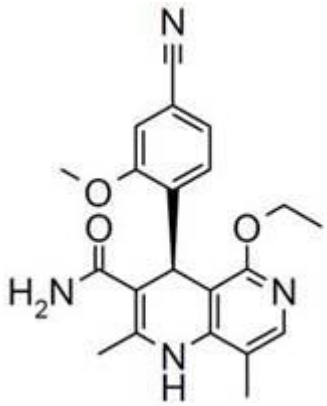
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	10 mg and 20 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	10 mg tablet: pink, oblong tablet with "FI" on one side of tablet, "10" on the other side of tablet. 20 mg tablet: yellow, oblong tablet with "FI" on one side of tablet, "20" on the other side of tablet.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Kerendia and finerenone	Adequate
Dosage form(s) and route(s) of administration	Tablet and Oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive ingredients of Kerendia are lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, hypromellose, magnesium stearate, and sodium lauryl sulfate. The film coating contains hypromellose, titanium dioxide and talc, in addition to ferric oxide red (10 mg) or ferric oxide yellow (20 mg) .	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	None	We let the clinical pharmacology team know to include the pharmacological class

Chemical name, structural formula, molecular weight	Finerenone's chemical name is (4S)-4-(4-cyano-2- methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide. The molecular formula is C21H22N4O3 and the molecular weight is 378.43 g/mol. The structural formula is: 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X,"	N/A	N/A

“structurally unique molecular entity”		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	10 mg and 20 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 30 and 90 counts	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Kerendia is available as a film-coated tablet in two strengths. The 10 mg is a pink oblong tablet with "FI" on one side of tablet and "10" on the other side of tablet. The 20 mg tablet is a yellow oblong tablet with "FI" on one side of tablet and "20" on the other side of tablet 30 counts, 0 mg, NDC 50419-540-01 90 counts, 10 mg, NDC 50419-540-02 30 counts, 20 mg, NDC 50419-541-01 90 counts, 20 mg, NDC 50419-541-02	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Excursions are permitted from 15°C to 30°C (59°F to 86°F)	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	None	The Applicant needs to include manufacturing information.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): None

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Kerendia® (finerenone) tablets	We let the DMEPA team know that the size of established name appears smaller than the half size of proprietary name.
Dosage strength	10 mg and 20 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	30 and 90 counts	Adequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	Present. See the container and carton labels	Adequate
Lot number and expiration date	Present. See the container and carton labels. No expiration date	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature].*	Store at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Excursions are permitted from 15°C to 30°C (59°F to 86°F)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Present. See the container and carton labels	Adequate

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor		Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D.; 3/31/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

David Claffey

Digitally signed by David Claffey
Date: 3/31/2021 04:07:32PM
GUID: 508da71e00029e20b201195abff380c2

Ali Mohamadi

Digitally signed by Ali Mohamadi
Date: 3/31/2021 03:16:30PM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e

39 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA: 215341

Drug Product Name / Strength: Kerendia (Finerenone film-coated Tablets) / 10mg, 20mg

Route of Administration: Oral

Applicant Name: Bayer

Review Summary:

The submission is seeking approval of Finerenone Tablets through 505 (b)(1) pathway, for the treatment of patients with chronic kidney disease and type 2 diabetes. Finerenone (BAY 94-8862) is a nonsteroidal mineralocorticoid receptor (MR) antagonist. The proposed starting dose is 10 mg or 20 mg, based on eGFR. The maximum daily dose of Kerendia is 20 mg.

Finerenone is formulated as immediate-release tablets with (b) (4) film coating for oral administration. The efficacy and safety of the proposed drug product was rested in a pivotal phase 3 randomized trial.

This Biopharmaceutics review is focused on the evaluation of data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) the bridging of the formulations used throughout development and the proposed commercial product. Based on the review of the provided information/data, the Division of Biopharmaceutics has the following assessment, conclusions and recommendations:

Dissolution Method and Acceptance criterion: The proposed dissolution method is found acceptable. To further mitigate the risk and to enhance the discriminating ability of the method, the Applicant tightened the acceptance criterion as per FDA recommendation. The tightened acceptance criterion together with the proposed dissolution method are able to reject the batches manufactured with drug substance having out-of-specification particle size (i.e., D90= (b) (4) µm).

Formulation Bridging: There is a minor difference (b) (4) between the proposed commercial formulation and the phase III formulation manufactured in commercial scale. Bridging between the two formulations are adequately supported by the dissolution data showing all batches conforming to the regulatory specifications. The Applicant provided comparative dissolution data for the clinical batches and the commercial batches, which further supported bridging.

Conclusions and Recommendations:

From a Biopharmaceutics perspective, NDA 215341 for Finerenone film-coated Tablets, 10 mg and 20 mg, are recommended for **APPROVAL**.

The FDA approved dissolution method and acceptance criterion are summarized in the following Table:

FDA Approved Dissolution Method and Acceptance Criterion for Quality Control (Finished Product Batch Release and Stability Testing) of Finerenone Film-Coated Tablets, 10mg and 20mg	
Apparatus	USP Apparatus II
Paddle Speed	75 rpm
Volume	900 mL
Medium	10 mg: Acetate buffer pH 4.5 20 mg: Acetate buffer pH 4.5 + 0.1% Tween 20
Temperature	37±0.5 ºC
Acceptance Criterion	Q (b) (4) % in 15 min

BIOPHARMACEUTICS ASSESSMENT

1. List Submissions being reviewed:

Sequence #	Submission	Date
0001	Original NDA	11/09/2020
0002	Response to IR	11/30/2020
0008	Response to OPQ IR	01/05/2021
0015	Response to OPQ IR	03/05/2021

Highlight Key Outstanding Issues from Last Cycle: None. First review cycle.

Concise Description Outstanding Issues Remaining: None. The NDA is ADEQUATE from a Biopharmaceutics perspective.

2. BCS Designation

No BCS designation request was submitted.

Solubility: low, as per BCS definition.

The crystalline drug substance Finerenone exists in only one modification, and is soluble to sparingly soluble at acidic pH (pH 1 and pH 2) and practically insoluble at pH 4.5 and neutral pH in aqueous media. The solubility data in difference media are shown in Table 1.

Table 1. Solubility of Finerenone in different media (pH, buffer salt and surfactant-level)

Medium		mg dissolved at 37 °C in 1000 mL	
Buffer system	Surfactant level	Values from late development	Values from early development
0.1 M HCl	0 %	approx. 5783	> 900
0.01 M HCl	0 %	approx. 1251	> 900
Acetate buffer pH 4.5	0 %	approx. 56	approx. 61
Acetate buffer pH 4.5	0.1 % Tween 20	approx. 65	approx. 98
Acetate buffer pH 4.5	0.1 % SDS	-	approx. 261
Phosphate buffer pH 6.8	0 %	approx. 24	approx. 35
Phosphate buffer pH 6.8	0.1 % Tween 20	-	approx. 56
Phosphate buffer pH 6.8	0.1 % SDS	-	approx. 102

Permeability: The Applicant claimed the permeability of finerenone is high. As per the proposed package insert[1], "Finerenone is completely absorbed after oral administration. (b) (4) (Cmax) (b) (4) between 0.5 and 1.25 hours after (b) (4) (b) (4)

[1] Proposed Package Insert. \\CDSESUB1\evsprod\nda215341\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-06nov2020.doc

3. Dissolution Method and Acceptance Criterion:

(1) Dissolution method development [2].

(b) (4)

[redacted]

[2] Dissolution method development report. \\CDSESUB1\evsprod\nda215341\0001\m3\32-body-data\32p-drug-prod\finerenone-coated-tablet-bayer\32p5-contr-drug-prod\32p53-val-analyt-proc\validation-analytical-procedures-9.pdf

(b) (4)

[redacted]

(2) Discriminating Ability of the Method

API Particle Size:

Finerenone tablets batches of all 3 dosages were manufactured with API both within (D90 (b) (4) [redacted] (b) (4)) and outside the proposed particle size specification (D90 > (b) (4) [redacted]). Dissolution

results in acetate buffer pH 4.5 are shown for the 5 mg and 10 mg tablets, and for the 20 mg tablets, dissolution data in acetate buffer + 0.1 % Tween 20 were collected.[3]
Tablets manufactured with API with particle sizes of D90 of (b) (4) show similar dissolution profiles, while particle sizes of (b) (4) lead to a slightly slower dissolution behavior. When using an API with a particle size of D90 of (b) (4) for the manufacture of Finerenone tablets, dissolution is significantly decreased with values of only around (b) (4) % at (b) (4) min. The influence of particle size of the API on the dissolution behavior of Finerenone tablets is similar for all 3 dosages.

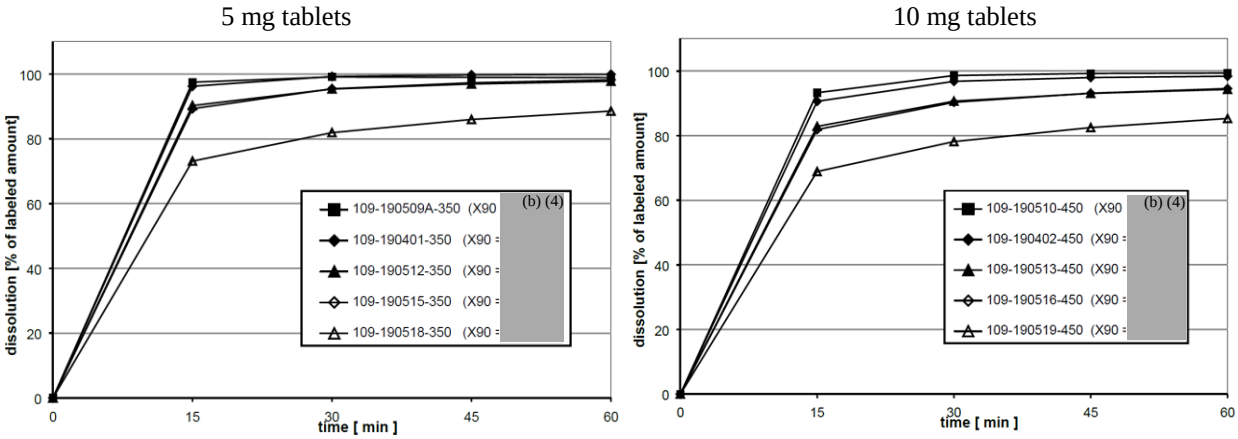


Figure 4: Discriminating ability of the dissolution method against different particle size of the API (acetate buffer pH 4.5, 75 rpm)

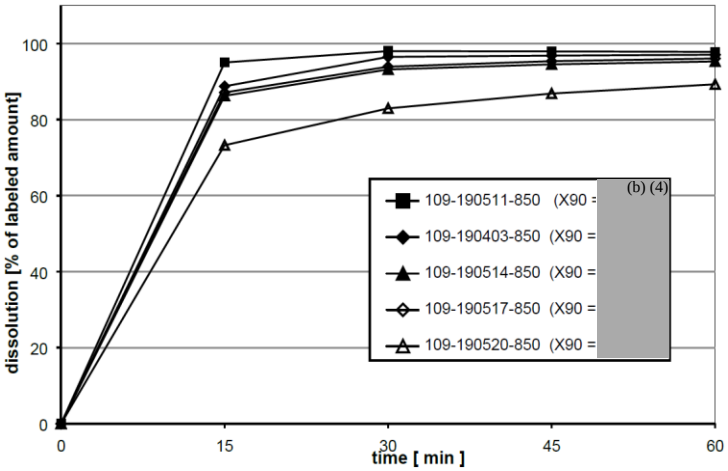


Figure 5: Discriminating ability of the dissolution method against different particle size of the API (acetate buffer pH 4.5 + 0.1 % Tween 20, 75 rpm, 20 mg tablets)

(b) (4)

[3] Excerpted from Figure 10, 11, and 12 of the method development report.

The dissolution profiles of the drug product [redacted] (b) (4) were compared. As expected, disintegration of tablets [redacted] (b) (4) is significantly delayed and consequently there is a lag time in dissolution. This effect is only small for the 5 mg tablet, due to the lower drug load, but more severe for the higher dosages of 10 mg and 20 mg.

Other parameters:
The [redacted] (b) (4), API concentration, and accelerated stability conditions were found to have no significant impact on dissolution.

Robustness:
The method is robust to the changes in temperature (37±2 ^{o}C), rotation speed (75±5 rpm), pH (4.5±0.2), and degassed or not degassed medium.[4]

Reviewer's Assessment:

The solubility of the drug substance is pH-dependent and considered low as per BCS guidance. The Applicant proposed to use pH 4.5 buffer as dissolution medium for 10 mg strength, and add 0.1% Tween in the medium for the 20 mg strength.
The proposed dissolution method together with the initially proposed acceptance criterion (NLT [redacted] (b) (4)% (Q) in [redacted] (b) (4) min) are not able to reject the batches manufactured with out-of-specification PSD specifically for 20mg strength. However, since the particle size of the API is controlled by the specification of the [redacted] (b) (4) drug substance with D90 ≤ [redacted] (b) (4) µm, manufacturing of DP batches with slower dissolution behavior is prevented. In addition, as per FDA recommendation based on the data obtained for the phase III batches, the Applicant tightened the dissolution acceptance criterion to Q=[redacted] (b) (4)% in 15 min, as discussed in the later section. The tightened acceptance criterion together with the proposed dissolution method helps to mitigate the risk and to enhance the discriminating ability of the method. Overall, the proposed dissolution method is found acceptable.

(3) **Dissolution Acceptance Criterion:**

[4] Page 26 to 34 of the method development report.

The dissolution profiles of three batches used for clinical phase III trials and of three primary stability batches that were manufactured in pilot scale are presented. Both the 20 mg strength[5] and 10 mg strength[6] showed very rapid (>85% in 15 min) dissolution.

In response to FDA's IR dated 12/10/2020, the Applicant further provided the dissolution data for the phase III batches that were manufactured in the commercial scale[7]. The tablets of both 10 and 20 mg strengths exhibited rapid dissolution with more than (b) (4)% released in 15 min.

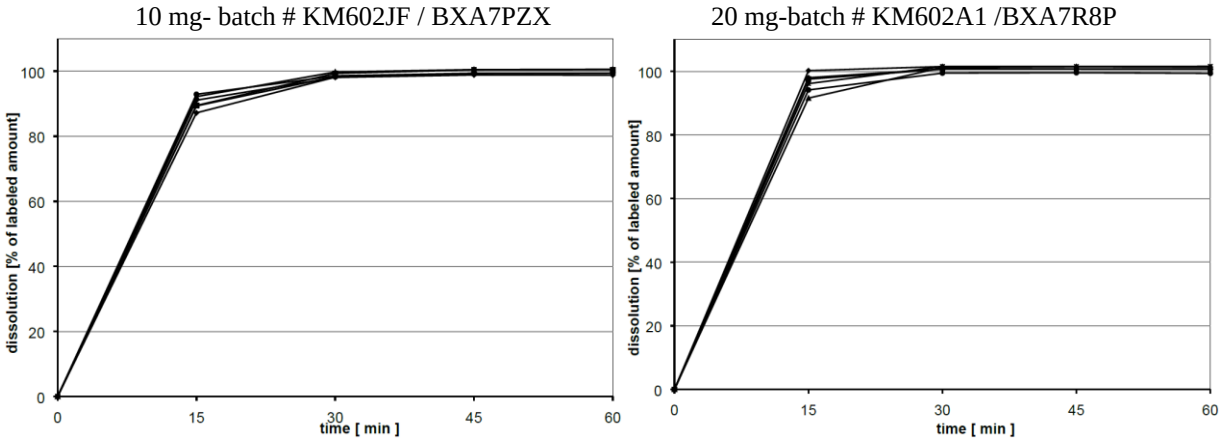


Figure 6. Representative Dissolution Profiles of Phase III Batches in Commercial Scale

Reviewer's Assessment:

The Applicant initially proposed an acceptance criterion of "Q=(b) (4)% in (b) (4)min". Based on the data provided, especially the data for the phase III batches manufactured in commercial scale, the acceptance criterion was revised to "Q=(b) (4)% in 15 min", as per FDA's recommendation conveyed in the IR letter dated 02/18/2021. The revised acceptance criterion is acceptable.

4. Bridging of Formulations

The clinical trials used two types of tablets (so called 'Phase I-IIa' and 'Phase IIb-III' formulation[8]) with similar qualitative composition of cores and manufacturing processes, but different shape, size and weight. A retrospective and pooled analysis, to be evaluated by OCP review team, compared finerenone AUC and C_{max} after dose-normalization in clinical

[5] Dissolution data for 20 mg batches used in Phase III trial and the stability batches manufactured in pilot scale. \\CDSESUB1\evsprod\nda215341\0001\m3\32-body-data\32p-drug-prod\finerenone-coated-tablet-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-p22020222854.pdf

[6] Dissolution data for 10 mg batches used in Phase III trial and the stability batches manufactured in pilot scale. \\CDSESUB1\evsprod\nda215341\0001\m3\32-body-data\32p-drug-prod\finerenone-coated-tablet-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-p22020222852.pdf

[7] Dissolution data for batches used in phase III trials and manufactured in commercial scale. \\CDSESUB1\evsprod\nda215341\0008\m3\32-body-data\32p-drug-prod\finerenone-coated-tablet-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-p22020229451.pdf

[8] See Appendix 3 for the composition of the formulations.

pharmacological studies, and the Applicant considered equivalent finerenone exposure, independent of the type of tablet applied (Module 5.3.5.3, Report PH-41449, Table 14.4/20)[9].

The batches used for phase IIb-III clinical trials were manufactured in both pilot scale [redacted] (b) (4) and commercial scale [redacted] (b) (4). Both core composition and [redacted] (b) (4) [redacted] (b) (4) are identical between the clinical Phase IIb-III formulation and proposed commercial products whereas differences exist [redacted] (b) (4) [redacted] (b) (4). The changes introduced [redacted] (b) (4) [redacted] (b) (4) are less than [redacted] (b) (4)%. As per SUPAC-IR, the change [redacted] (b) (4) is considered Level-1 composition change, and no additional in vitro or in vivo bridging data is needed, except that the commercial drug product is expected to meet the drug product dissolution specifications. Furthermore, the Applicant provided comparative dissolution profiles of the clinical batches and the commercial product which supported similarity (Figure 7).

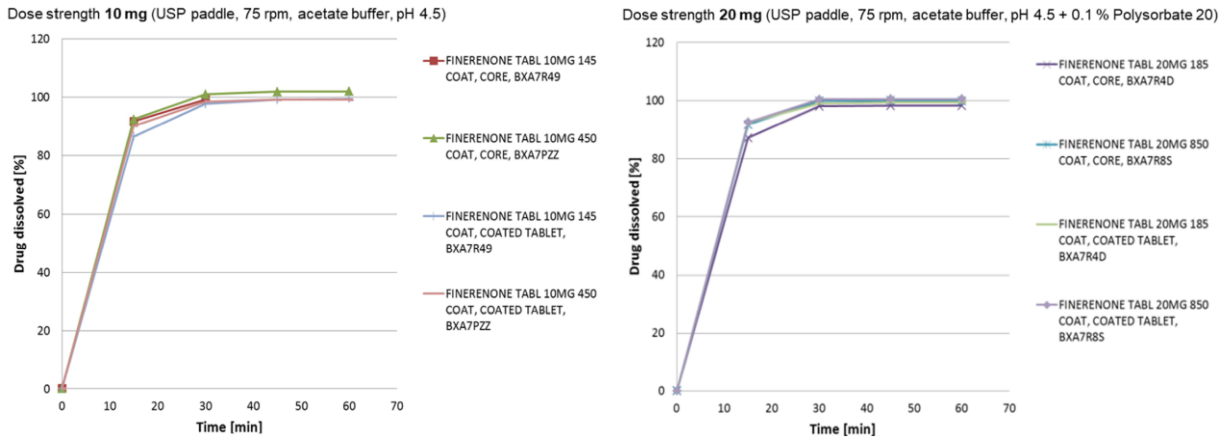


Figure 7.[10] Comparison of dissolution profiles of finerenone film-coated tablets manufactured in commercial scale (clinical samples [redacted] (b) (4) and commercial product [redacted] (b) (4) mean values of n=6

The stability/registration batches have exactly the same composition as the proposed commercial product except for [redacted] (b) (4). The manufacturing scale is also different, with the stability batches in pilot scale [redacted] (b) (4) and there is a 6.25X scale-up for commercial batches [redacted] (b) (4)). The minor difference [redacted] (b) (4) and Level-1 scale change does not require additional bridging data. In addition, the acceptance criterion was set primarily based on the data for the phase III batches.

[9] From page 368 of \\CDSESUB1\evsprod\nda215341\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ckd-and-t2d\5353-rep-analys-data-more-one-stud\20921\20921-study-report.pdf

[10] From Page 13 of \\CDSESUB1\evsprod\nda215341\0001\m2\27-clin-sum\summary-biopharm.pdf

It is noted that Bayer and the FDA had a Type C meeting on 12 Dec 2017 to explore the [redacted] (b) (4) manufacturing process for finerenone[11]. However, at the time of this NDA, Bayer is not considering implementing the [redacted] (b) (4) process. Therefore all the phase III clinical batches, stability batches, and the proposed commercial batches were manufactured [redacted] (b) (4). There is no difference in manufacturing process among different formulations, [redacted] (b) (4).

Reviewer's Assessment:

There is no difference in scale and process between some of the formulations tested in phase 3 clinical trial and the proposed commercial formulation, and the difference in [redacted] (b) (4) *formulation is Level 1 change based on SUPAC-IR. The bridging is supported by all batches conforming to the regulatory specifications, and the comparative dissolution data.*

5. *Biowaiver Request*

No Biowaiver request was submitted, nor needed. Both the 10 mg and 20 mg strengths tablets manufactured in commercial scale were used in the pivotal phase III efficacy and safety trials.

6. List of Deficiencies: **None.**

Primary Biopharmaceutics Reviewer Name: *Jing Li, Ph.D.*

Secondary Reviewer Name (and Secondary Summary, as needed): *Poonam Delvadia, Ph.D.*

[11] Meeting minutes dated 01/12/2018. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80478487&_afrRedirect=2399812405378049

APPENDIX 1. Biopharmaceutics IR #1 (dated 12/10/2020) and The Applicant's Response

Biopharmaceutics IR #1 Dated 12/10/2020[12]:

It is noted that on Page 6 of "Pharmaceutical Development-Drug Product (P.2.2.01-01)", you stated "Finerenone coated tablets for Phase III clinical trials were manufactured in pilot scale and in commercial scale". However, the information of the Phase III batches manufactured at the commercial scale cannot be located in the NDA. Provide the batch information and the complete multi-point dissolution profile data (individual, mean, CV%, profile) for the Phase III batches manufactured at the commercial scale.

The Applicant's Response Received on 01/05/2021:

\\CDSESUB1\evsprod\nda215341\0008\m1\us\12-cover-letters\response-to-fda-request-for-information.pdf Page 6.

[12] \\CDSESUB1\evsprod\nda215341\0008\m1\us\12-cover-letters\fda-request-for-information.pdf

APPENDIX 2. Biopharmaceutics IR #2 (dated 02/18/2021)[13] and the Applicant's Response

Biopharmaceutics IR #2 Dated 02/18/2021:

Based on the dissolution data you provided for the batches that were used in phase III clinical trial, we recommend that you implement the dissolution acceptance criterion of "Q= (b) (4)% in 15 min" for both the 10 mg and 20 mg of Finerenone tablets. Update your drug product release and stability specifications accordingly. Note that setting of the dissolution acceptance criterion is based on stage 2 testing (n=12), and therefore sometimes stage 2 testing and occasional stage 3 testing may be needed.
Also note that the tightened acceptance criterion together with your proposed dissolution methods improve the discriminating ability of the test; specifically, it will be able to reject the batches manufactured with drug substance having D90 of (b) (4) µm, which could not be rejected by your currently proposed dissolution method and acceptance criterion.

The Applicant's Response Dated 03/05/2021:

\\CDSESUB1\evsprod\nda215341\0015\m1\us\12-cover-letters\response-to-information-request.pdf Page 11.

[13] \\CDSESUB1\evsprod\nda215341\0015\m1\us\12-cover-letters\information-request-18feb2021.pdf

APPENDIX 3. Drug Product Composition[14]

Composition of the Phase IIb/III formulation.

	[mg/tablet]
Tablet core	(b) (4)
Finerenone (b) (4)	
Cellulose microcrystalline	
Croscarmellose sodium	
Hypromellose (b) (4)	
Lactose monohydrate	
Magnesium stearate	
Sodium laurilsulfate	
Weight (tablet core)	
Film-coating	
Hypromellose (b) (4)	
Talcum	
Titanium dioxide	
Ferric oxide red	
Ferric oxide yellow	
Weight (film-coating)	
Weight (coated tablet)	

Composition of the Proposed commercial formulation*

Dose [mg]	5	10	20
Tablet core			
Finerenone (b) (4)	5.00	10.00	20.00
Cellulose microcrystalline	(b) (4)		
Croscarmellose sodium			
Hypromellose (b) (4)			
Lactose monohydrate			
Magnesium stearate			
Sodium laurilsulfate			
Weight (tablet core)			
Film-coating			
(b) (4)			
Hypromellose (b) (4)			
(b) (4)			
Ferric oxide red			
Ferric oxide yellow			
Talc			
Titanium dioxide			
Weight (film-coating)			
Weight (coated tablet)			

* The Applicant is seeking approval only for 10mg and 20mg strengths

[14] Excerpted from Table 20 and 21 of the PDR. \\CDSESUB1\evsprod\nda215341\0001\m3\32-body-data\32p-drug-prod\finerenone-coated-tablet-bayer\32p2-pharm-dev\pharmaceutical-development-drug-product-p2201022238913-finer.pdf

Jing Li

Digitally signed by Jing Li
Date: 3/29/2021 02:51:51PM
GUID: 508da7420002bb05ac913303b23c39bb

Poonam Delvadia

Digitally signed by Poonam Delvadia
Date: 3/29/2021 02:58:03PM
GUID: 5388edae000671a12787e2fcf4cde1bb

Mohan Sapru

Digitally signed by Mohan Sapru
Date: 5/14/2021 04:25:47PM
GUID: 504f821600000ec6d20b59d2b68eb3d2